REMARKS/ARGUMENTS

Status of the Claims

After entry of the above amendments, claims 1-9 and 33-41 are pending. Claims 1, 4 and 33 are amended.

Amended claims 1 and 33 now recite a "constitutive androstane receptor (CAR)-mediated disorder or condition that involves aberrant cholesterol levels." Support is found on page 15, line 23 of the specification. Claim 33 has also been amended to recite a "CAR compromised mammal" in the second instance so that it is now consistent with the first recitation of "CAR compromised mammal." Claim 4 has been amended to recite "test" mammal so that it is now consistent with claims 1 and 5. No new matter has been added by the foregoing amendments.

The specification is amended at the paragraph bridging pages 17-18 to remove the hyperlink designator "http://" and to correct a typographical error.

Objection to the Specification

Pursuant to M.P.E.P. § 608.01, the Examiner objects to the specification for reciting a browser-executable hyperlink on page 17, line 27. Applicants obviate this objection by removing the hyperlink designator "http://." The specification now recites a URL address which is not browser-executable, and which is not intended to be an active hyperlink.

Rejection of Claims 1-9 and 33-41 under 35 U.S.C. § 112, Enablement

The Examiner has rejected Claims 1-9 and 33-41, because independent claims 1 and 33 are allegedly not enabled for identifying agents that affect all CAR-related diseases. Applicants respectfully traverse this rejection because the specification enables those skilled in the art to practice the claimed methods.

As amended, independent claims 1 and 33 now recite methods for identifying a therapeutic agent for treating a constitutive androstane receptor (CAR)-mediated disorder or

condition *that involves aberrant cholesterol levels*. The scope of the amended claims is not directed to all constitutive androstane receptor (CAR)-mediated disorders or conditions, but to those that involve aberrant cholesterol levels, thus addressing the Examiner's concern raised on page 3 of paper 18). The Examiner concedes that Applicants teach that disruption of CAR function results in elevated plasma cholesterol levels (hypercholesterolemia) (*see*, page 3 of paper 18). Applicants respectfully assert that one of skill in the art could predictably use effects on cholesterol as a means of identifying therapeutic agents for treating a CAR-mediated disorder or condition that involves aberrant cholesterol levels. This is because determining the modulation of a cholesterol indicator is a logical correlative factor for identifying therapeutic agents that modulate a CAR-mediated intermolecular interaction and which are useful for treating a CAR-mediated disorder or condition that involves aberrant cholesterol levels. Likewise, effects on cholesterol is also a predictable means of identifying a therapeutic agent for treating a CAR-mediated disorder or condition that involves aberrant cholesterol levels in a CAR-compromised mammal. This is because determining a change in cholesterol levels is a logical correlative factor for identifying therapeutic agents for treating a CAR-mediated disorder or condition that involves aberrant cholesterol levels in a CAR-compromised mammal.

The Examiner states that the diseases recited in Claim 4, presumably intending Claim 3, do not predictably relate to CAR (page 3 of paper 18). Claim 3 recites that the CAR-mediated disorder or condition that involves aberrant cholesterol levels is hypercholesterolemia, lipid disorders, atherosclerosis or cardiovascular disease. Applicants respectfully assert that hypercholesterolemia, lipid disorders, atherosclerosis or cardiovascular disease are conditions that can inherently involve aberrant levels of cholesterol, and which can be predictably treated by therapeutic agents that lower elevated plasma cholesterol by modulating a CAR-mediated intermolecular interaction.

Attached to this response as Exhibit A is Chapter 36, entitled "Drugs used in the treatment of hyperlipoproteinemias," from Goodman and Gilman's *The Pharmacological Basis of Therapeutics*, 9th Ed. (1996) (hereafter "Goodman"). On page 875, Goodman states that hyperlipidemia, a lipid disorder, involves elevated plasma levels of triglycerides and cholesterol

(*see also*, page 894). Page 875 of Goodman further discusses as a matter of introduction the cause-and-effect relationship between hypercholesterolemia and coronary artery disease (CAD), a cardiovascular disease which is associated with atherosclerosis (*see*, page 879). Page 878 of Goodman discusses the intrinsic relationship between hypercholesterolemia and low density lipoproteins (LDL), and states that LDL normally accounts for two-thirds of plasma cholesterol content (*see*, page 877). Importantly, the favored drugs for treating lipid disorders, cardiovascular disorders and atherosclerosis associated with elevated plasma levels of LDL and consequent hypercholesterolemia are those that lower plasma LDL (and hence, cholesterol) levels by interfering with cholesterol synthesis or promoting LDL clearance (*see*, page 883). For instance, the drugs useful for treating hypercholesterolemia by lowering LDL levels, HMG CoA reductase inhibitors, function by blocking the synthesis of cholesterol in the liver (*see*, pages 883 and 885). An alternative choice of drugs, bile acid-binding resins, function by increasing the conversion of cholesterol to bile acids (*see*, page 888). Nicotinic acid and Probucol also decrease plasma LDL, most likely by increasing clearance of LDL and LDL precursors (*see*, pages 890 and 891). Fibric acid derivatives may also inhibit cholesterol synthesis in some patients (*see*, page 893).

It is clear from the disclosure of Goodman that lipid disorders, atherosclerosis and cardiovascular disease due to elevated LDL are conditions that inherently involve aberrant levels of cholesterol. Regardless of the etiology of elevated plasma LDL (cholesterol), the drug treatments described in Goodman Chapter 36 seek to achieve the pharmacologically common goal of lowering plasma LDL (and cholesterol) levels through a variety of different mechanisms. The present methods modulate plasma cholesterol levels through a CAR-mediated mechanism. Therefore, one of skill in the art could reasonably identify without undue experimentation a therapeutic agent for use in treating a CAR-mediated disorder or condition that involves aberrant cholesterol levels, such as hypercholesterolemia, lipid disorders, atherosclerosis or cardiovascular disease, by administering to a test mammal a compound that can modulate a CAR-mediated intermolecular interaction and then determining whether a cholesterol indicator is modulated (*e.g.*, increase or decrease).

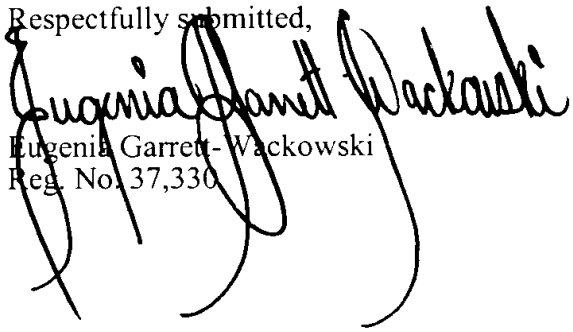
For the foregoing reasons, Applicants respectfully assert that the specification enables those skilled in the art to practice the methods of identifying a therapeutic agent for use in treating a CAR-mediated disorder or condition that involves aberrant cholesterol levels. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



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Attachments
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